

Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of breast, lung, and testicular cancer.

The adverse effects of systemic chemotherapy used
5 in the treatment of neoplastic disease is most feared by patients undergoing treatment for cancer. Of these adverse effects nausea and vomiting are the most common and severe side effects. Other adverse side effects include cytopenia, infection, cachexia, mucositis in
10 patients receiving high doses of chemotherapy with bone marrow rescue or radiation therapy; alopecia (hair loss); cutaneous complications (see M.D. Abeloff, et al: Alopecia and Cutaneous Complications. P. 755-56. In Abeloff, M.D., Armitage, J.O., Lichter, A.S., and
15 Niederhuber, J.E. (eds) Clinical Oncology. Churchill Livingston, New York, 1992, for cutaneous reactions to chemotherapy agents), such as pruritis, urticaria, and angioedema; neurological complications; pulmonary and cardiac complications in patients receiving radiation or
20 chemotherapy; and reproductive and endocrine complications.

Chemotherapy-induced side effects significantly impact the quality of life of the patient and may dramatically influence patient compliance with
25 treatment.

Additionally, adverse side effects associated with chemotherapeutic agents are generally the major dose-limiting toxicity (DLT) in the administration of these drugs. For example, mucositis, is one of the major dose
30 limiting toxicity for several anticancer agents, including the antimetabolite cytotoxic agents 5-FU, methotrexate, and antitumor antibiotics, such as

-4-

doxorubicin. Many of these chemotherapy-induced side effects if severe, may lead to hospitalization, or require treatment with analgesics for the treatment of pain.

5 The adverse side effects induced by chemotherapeutic agents and radiation therapy have become of major importance to the clinical management of cancer patients.

FR 27 71 005 describes compositions containing a
10 cyclooxygenase-2 inhibitor and a N-methyl-d-aspartate (NMDA) antagonist used to treat cancer and other diseases.

WO 99/18960 describes a combination comprising a
15 cyclooxygenase-2 inhibitor and an induced nitric-oxide synthase inhibitor (iNOS) that can be used to treat colorectal and breast cancer.

WO 99/13799 describes the combination of a cyclooxygenase-2 inhibitor and an opioid analgesic.

WO 98/41511 describes 5-(4-sulphunyl-phenyl)-
20 pyridazinone derivatives used for treating cancer.

WO 98/41516 describes (methylsulphonyl)phenyl-2-(5H)-furanone derivatives that can be used in the treatment of cancer.

WO 98/16227 describes the use of cyclooxygenase-2
25 inhibitors in the treatment or prevention of neoplasia.

WO 97/36497 describes a combination comprising a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor useful in treating cancer.

WO 97/29776 describes a composition comprising a
30 cyclooxygenase-2 inhibitor in combination with a leukotriene B4 receptor antagonist and an immunosuppressive drug.

WO 97/29775 describes the use of a cyclooxygenase-2 inhibitor in combination with a leukotriene A4 hydrolase inhibitor and an immunosuppressive drug.

WO 97/29774 describes the combination of a
5 cyclooxygenase-2 inhibitor and protstaglandin or antiulcer agent useful in treating cancer.

WO 97/11701 describes a combination comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist useful in treating colorectal cancer.

10 WO 96/41645 describes a combination comprising a cyclooxygenase-2 inhibitor and a leukotriene A hydrolase inhibitor.

WO 96/03385 describes 3,4,-Di substituted pyrazole compounds given alone or in combination with NSAIDs,
15 steroids, 5-LO inhibitors, LTB4 antagonists, or LTA4 hydrolase inhibitors that may be useful in the treatment of cancer.

WO 98/47890 describes substituted benzopyran derivatives that may be used alone or in combination
20 with other active principles.

WO 98/16227 describes a method of using cyclooxygenase-2 inhibitors in the treatment and prevention of neoplasia.

U.S. Patent No. 5,854,205 describes an isolated
25 endostatin protein that is an inhibitor of endothelial cell proliferation and angiogenesis.

U.S. Patent No. 5,843,925 describes a method for inhibiting angiogenesis and endothelial cell proliferation using a 7-[substituted amino]-9-
30 [(substituted glycyloamido)-6-demethyl-6-deoxytetracycline.